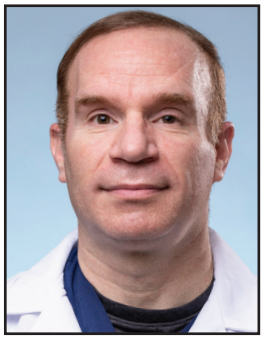
Douglas G. Adler MD, FACG, AGAF, FASGE, Series Editor

Endohepatology: A New Realm for Endoscopic Ultrasound

Byron Marciniak



Douglas G. Adler

INTRODUCTION

With advancements in endoscopic ultrasound (EUS) and its expanding role in management of liver disease, has come a new field that has been termed **Endohepatology**. Traditionally, liver disease and its comorbidities have been inspected by interventional radiology using percutaneous methods. With the emergence of the field of endohepatology, EUS-guided alternatives to the traditional percutaneous routes for procedures such as liver biopsy (LB), portal pressure measurement, and treatment of gastric varices have been developed and have entered practice. This manuscript will review the current state of endohepatology, discuss endoscopic diagnostic and therapeutic tools and techniques, and analyze the data comparing traditional methods to new endoscopic methods of diagnosis and treatment of patients with liver disease.

EUS Guided Liver Biopsy

EUS-LB is a unique approach to liver biopsy because of its ability to obtain samples from the liver without traversing the skin. EUS-LB is performed using a standard linear echoendoscope which provides high-quality, real-time views of the liver and surrounding solid and vascular structures. This allows for precise needle placement in both normal liver parenchyma and, on some occasions, liver lesions. Doppler ultrasound also prevents injury to interposed vascular structures.[1]

EUS-LB is typically performed using either a 19-gauge or a 22-gauge needle, although most practitioners utilize a 19-gauge needle as it provides a much larger and less fragmented sample.[2] (Figure 1 and Figure 2) A variety of approaches and techniques are available, but many centers utilize the technique proposed by Diehl et al. using heparinized needles with wet suction.[3] Typically, studies of EUS-LB specimens compare efficacy of needle sizes and models by assessing the tissue obtained via their use. Studies compare length of the longest piece (LLP), intact specimen length (ISL), total specimen length (TSL), the number of complete portal triads (CPTs), tissue adequacy, and adverse events.

A recent study comparing a 19G fine-needle aspiration device (FNA) to 22G fine-needle biopsy (FNB) showed a tissue adequacy, measured by number of portal structures in the sample, of 88% in 19G FNA vs. 68% in 22G FNB.[2] It was found that since the 22G FNB produced thinner samples than

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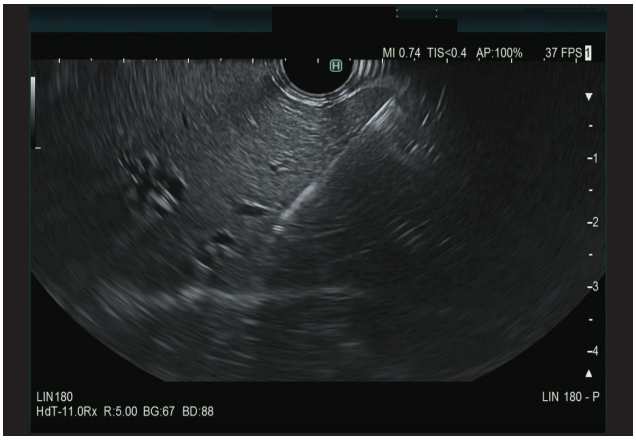

Figure 1. 7.5 MHz image of an EUS-guided liver biopsy using a 19g needle

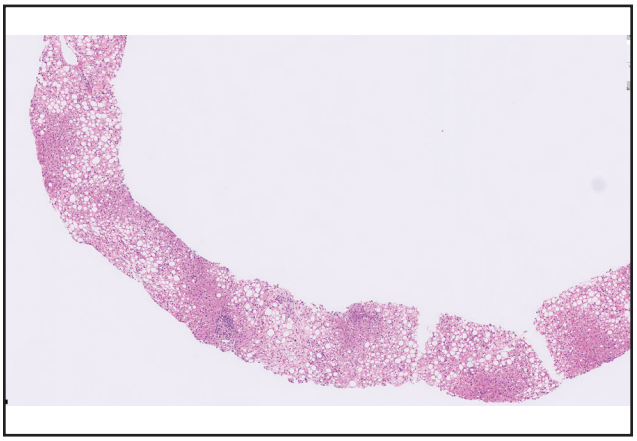

Figure 2a. Medium power image of an EUS-guided liver biopsy showing long specimen length

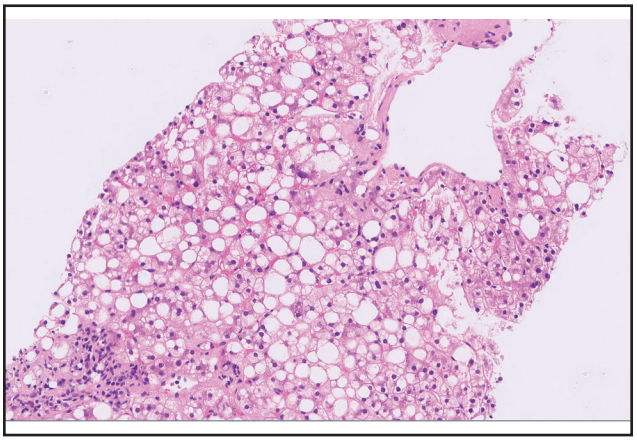

Figure 2b. High power image of the same EUS-guided liver biopsy as Figure 1a showing ballooning degeneration and Mallory bodies consistent with steatohepatitis

the 19G FNA, they were prone to fragmentation during tissue processing.

There are several different techniques for EUS-LB. For retrieving the sample, there is a "slow pull" technique, as well as a "wet suction" technique, and they are often combined in practice. The "slow pull" technique uses minimal suction via the gradual removal of the stylet during the needle actuations and is useful in collecting samples with less blood and more tissue. The "wet suction" technique involves flushing the needle with saline or, more commonly, heparin with the addition of suction. It was found that priming the needle with an anticoagulant had no adverse effects on the sample and helped to resolve the issue of blood collection and reduced sample fragmentation.[3,4]

Other traditional methods of liver biopsy include the Percutaneous route (PC) and the Transjugular route (TJ). The PC route uses spring-loaded 18G, 19G, or 20G needles, while the TJ route uses either an 18G or 19G needle.[5] One of the primary concerns with EUS-LB was that the limitations of needle size to 19G would produce smaller and lower quality samples than the other two routes. However, when EUS-LB was compared to PC and TJ routes, it was found that EUS-LB produced more tissue with a greater TSL. The number of CPTs were greater in the EUS-LB samples than PC, but equivalent to TJ.[5] Once rarely performed, EUS-LB is now entering widespread usage in the United States.

In one study, diagnostic accuracy was found to be similar between EUS-LB and PC-LB.[6] This study found a diagnostic adequacy rate of 100% in PC-LB and 94.4% in EUS-LB ($p = 0.74$); the study also showed a diagnostic accuracy rate of 100% in PC-LB and 88.8% in EUS-LB ($p = 0.82$). Another study comparing PC-LB and EUS-LB showed a sensitivity, specificity, and accuracy of 95%, 100%, and 96% in the PC group and 100%, 100%, and 100% in the EUS group, respectively, showing no significant difference.[7]

Adverse events associated with EUS, PC, and TJ liver biopsy include pain, intraperitoneal and subcapsular hemorrhage, bile peritonitis, inadvertent sampling of other organs, pneumothorax, and infection.[5] There has been conflicting evidence with regards to adverse event rates between EUS-LB and PC-LB.[8,9]

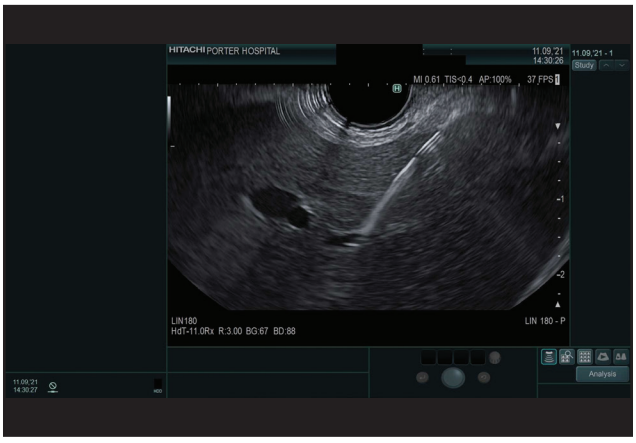

Figure 3. 7.5MHz EUS image of measurement needle in the hepatic vein during EUS-guided portal pressure measurement

One study has shown adverse event rates of 17% in patients undergoing PC-LB versus 2% among patients undergoing EUS-LB ($p< 0.01$).[8] However, another study showed that adverse event rates in both PC-LB and EUS-LB were 0%, although this may be an outlier in both respects.[9] Studies done separately from one another have also shown that liver biopsy via EUS, PC, and TJ routes all have similar adverse event rates. A meta-analysis performed to assess the efficacy and safety of EUS-LB found across 8 studies a pooled adverse event rate of 2.3%.[10] A study on PC-LB showed adverse event rates between 0.09% and 3.1%, and another study on TJ-LB had adverse event rates between 0.56% and 6.5%.[11,12]

There are several variations in needle models, size, and tip design. The options for EUS-LB needle tip design include: Franseen-Type, a needle with 3 cutting tips; Fork-Tip-Type, a needle with 2 parallel cutting tips; Menghini-Type, a needle with a beveled end cutting edge; and the ProCore, a needle with an end cutting beveled edge and a core trap near the tip.[13] A study comparing these models found that all samples obtained with 19G and 20G needles, regardless of model, had statistically similar mean numbers of CPTs. It also found that yields of the 19G and 20G needles were statistically superior to the 22G SharkCore Fork-Tip-Type needle, further suggesting the inadequacy of 22G needles for EUS-LB. This study found statistically significant evidence that the Acquire Franseen-Type 19G needle produced longer tissue fragments than all the other needle types tested, except for the EZ Shot 3 Plus Menghini-Type 19G needle.[13]

Three studies have compared the Franseen-Type needle design to the Fork-Tip-Type. Across these studies, Franseen-Type needles had a statistically significant higher number of CPTs than the Fork-Tip-Type needle (14.4 vs. 9.5 with $p = 0.043$; 9.59 vs. 7.07 with a $p < 0.001$; 24.0 vs. 19.5 with a $p < 0.01$).[14,15,16] When comparing specimen length and histological adequacy, there are conflicting findings. Of these 3 studies, 2 found that the Franseen-Type had statistically significant longer specimen length (15.81mm vs. 13.86mm with $p = 0.004$; 31mm vs. 27mm with $p = 0.01$).[15,16] The remaining study found no significant difference in specimen length (44.9mm vs. 34.6mm with $p = 0.097$).[14] Two of these studies also compared histological adequacy of the tissue samples collected. One study showed no statistically significant difference between the two needles with adequacy at 100% in the Franseen-Type and 95.5% in the Fork-Tip-Type ($p = 0.312$).[14] The other study, however, showed a histologic adequacy of 97.2% in the Franseen-Type and 79.4% in the Fork-Tip-Type ($p = 0.001$).[15]

EUS Guided Portal Pressure Measurement

The portal pressure gradient (PPG) is a measurement that is useful in assessing the degree of portal hypertension (PH) and the severity of cirrhosis. Currently, the standard for PH assessment is the use of an indirect PC method that measures the hepatic venous pressure gradient (HVPG) via a transjugular approach.[17]

EUS-guided portal vein pressure (PVP) measurement is performed using a linear echoendoscope, a 25G needle, and a compact, one-time-use pressure manometer with non-compressible tubing.[18] To calculate the PPG, pressure measurements need to be made in both the hepatic vein (HV) and portal vein (PV), and then the HV pressure is subtracted from the PV pressure. Access to the HV is possible by first identifying the inferior vena cava (IVC), with the echoendoscope located at the gastroesophageal junction. Any of the three hepatic vein branches can be used for measurement after identification.[18] (Figure 3) The PV pressure measurement is made

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in the intrahepatic PV near the PV bifurcation. (Figure 4) Manometry of the PV is performed usually with a transgastric approach. However, an alternative transduodenal, transhepatic approach can be utilized as well.[18]

Studies performed that compared the EUS-PPG measurement to indirect TJ HVPG measurement have found no statistically significant difference in accuracy.[19] In one study, each participant had their PVP measured first with the EUS-PPG method, followed by the indirect TJ method. When PVP values from each method were compared in a linear relationship, a Pearson's correlation coefficient of 0.923 and 95% confidence interval (CI) of 0.6369 to 0.9821; and an R^2 value of 0.852; was found. This shows remarkable consistency between the two methods. Similarly, when comparing the mean PVP findings between the two methods, they also found no significant difference ($p = 0.231$).[19] Another comparison study had similar results. The study found that the Pearson's correlation coefficient was 0.999 for all vessels, 0.985 for all veins, 0.988 for PV and wedged hepatic venous pressure, and 0.986 for free HV pressure.[20] It should be noted that the PVP obtained by interventional radiologists is indirect, as it is a wedged pressure obtained in the HV, but during EUS-PPG the PVP is, in fact, measured directly.

It was also found that EUS-PPG and indirect TJ HVPG do not have a statistically significant difference in procedure time. In one study, the average procedure time for EUS-PPG was 38.33 minutes; for indirect TJ HVPG it was 37.22 minutes ($p = 0.862$).[19] EUS-PPG has shown specific benefit in the measurement of PVP in patients with Budd-Chiari syndrome (hepatic vein occlusion subtype). In one study, 2 of the participants were diagnosed with Budd-Chiari syndrome. For these participants, it was not possible to obtain PVP using the indirect TJ method, however, EUS-PPG was still measured successfully.[19]

Adverse events with either method include bleeding, infection, thrombosis, or perforation. Across 5 studies, no adverse events were recorded with EUS-PPG, nor the indirect TJ method.[19,20,21,22,23]

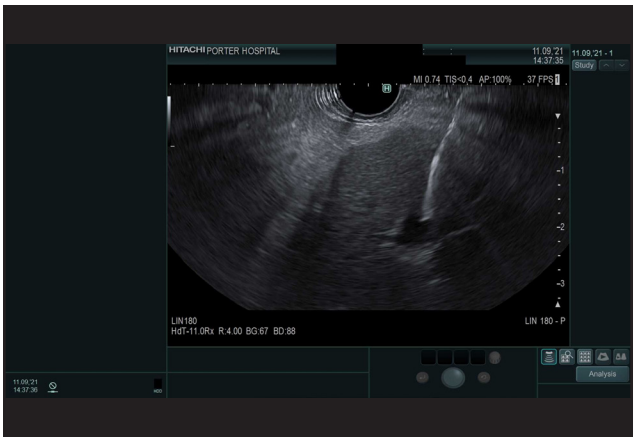

Figure 4. 7.5MHz EUS image of measurement needle in the portal vein during EUS-guided portal pressure measurement

EUS Guided Gastric Variceal Coiling and Gluing

There are three different classification systems commonly used for gastric varices (GV): Sarin's classification, Hashizome's classification, and Arakawa's classification. Sarin's classification is the most commonly used method.[24] In this system, GVs are categorized into 4 types based on location and relationship with esophageal varices (EV). Types include gastroesophageal varices (GOV) Type 1 and 2, and isolated gastric varices (IGV) Type 1 and 2. GOV type 1 is described as EVs that extend down the lesser curvature of the stomach, whereas GOV type 2 is described as EVs that extend down the greater curvature of the stomach. Type 1 IGV are GVs that exist exclusively in the fundus of the stomach, whereas IGV type 2 is defined as ectopic varices that occur in other parts of the stomach or duodenum.[24,25]

In one study, GVs were present in 20% of patients with PH at initial evaluation. The incidence of bleeding was greatest in IGV type 1 at 78%. When compared with isolated EVs, GVs bled in significantly fewer patients (64% vs. 25%). Although GVs had a lower bleeding risk than EVs, when they did bleed it was more severe. In this study, a bleeding GV was found to have a high mortality rate of 45%.[25]

Treatment options for GVs include endoscopic sclerotherapy, endoscopic variceal ligation (EVL), endoscopic variceal obturation with tissue adhesive such as cyanoacrylate glue (CYA), fibrin

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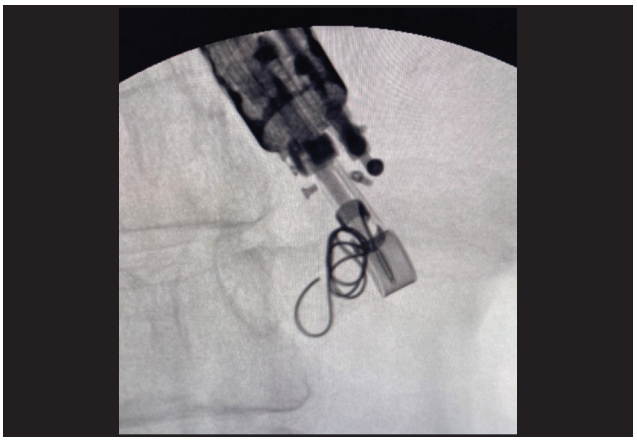

Figure 5. Fluoroscopic image of EUS-guided coil delivery to treat a gastric varix

glue, or thrombin, EUS-guided coil deployment, balloon tamponade, a transjugular intrahepatic portosystemic shunt (TIPS) procedure, or balloon-occluded retrograde transvenous obliteration (BRTO).[26,27,28] TIPS is the most commonly performed procedure for GVs secondary to portal hypertension. The preferred initial endoscopic treatment option is cyanoacrylate glue or fibrin injection and/or coil deployment.[27,28] (Figure 5) Approaches in practice remain nonstandardized.

Glue injection can be performed with either direct endoscopy or under the guidance of EUS. A recent comparative study showed that EUS-guided glue injection required less glue and had decreased rebleeding rates, with no significant difference in adverse events, when compared with direct endoscopic glue injection.[29]

CYA glue has multiple monomers available for use, including N-butyl-2-cyanoacrylate (NB2-CYA) and 2-octyl-cyanoacrylate (2O-CYA). What makes each monomer unique is the size of their alkyl group; NB2-CYA has a 4-carbon alkyl group, whereas 2O-CYA has an 8-carbon alkyl group.[26] The longer the alkyl group, the longer the polymerization time of the glue will be. The polymerization time for NB2-CYA is so short it can cause premature solidification of glue inside a delivery needle or within a varix, risking entrapment of the needle. To prevent premature solidification of the glue, NB2-CYA is diluted with Lipiodol. Since 2O-CYA has a longer polymerization time, dilution is not required.[26] As an alternative to CYA glue injection, one could also use absorbable gelatin sponge (AGS) in the treatment of GVs. AGS is a purified collagen that forms a plug by absorbing 45 times its volume in blood.[30]

EUS-guided coil deployment utilizes stainless steel micro-coils that reduce the rate of blood flow and promote thrombosis of the varix.[28] When coil and glue monotherapy have been compared, it has been shown that they share similar hemostasis rates and have no significant difference in the number of sessions required for obliteration ($p = 0.29$).[29] Coils do however, have statistically significant fewer adverse events when compared to glue injection ($p < 0.1$).[29]

It has been found that when glue injection and coil deployment are combined it is more efficient than either alone, with decreased recurrence rates, volumes of glue, and numbers of coils required.[31,32] One study also showed that combination therapy had statistically significant higher rates of technical and clinical success than either alone ($p < 0.001$).[32]

Potential adverse events from the use of CYA glue, thrombin injection, or coil deployment include pulmonary or systemic embolization, visceral fistulization, ulceration and bleeding at the injection site, peritonitis, needle impaction, traumatic withdrawal due to glue adherence to the needle, coil extrusion, and death.[26,32,33] One study compared glue and coil monotherapy and found that adverse event rates were statistically significantly higher with CYA glue injection (58%) than coil (9%) deployment ($p < 0.01$).[26] Another study that compared glue and coil combination therapy with each of these agents as monotherapy found that combination therapy had statistically significant fewer adverse events than glue monotherapy (10% vs. 21%; $p < 0.001$). This same study also found that combination therapy did not have a statistically significant difference in adverse event rates when compared with coil monotherapy (10% vs. 3%; $p = 0.057$).[32]

CONCLUSION

Endohepatology is an emerging field with novel, minimally invasive diagnostic and therapeutic options for patients with liver disease. EUS guided liver biopsy, portal pressure measurement, and gastric variceal treatment are commercially available and remain targets of active investigation

as promising alternatives to the current standard of care. Future studies will likely further refine the role of these interventions. ■

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Answers to this month's crossword puzzle:

1 E	R	2 O	S	3 I	V	4 E	■	5 R	A	6 D	I	7 A	T	8 E
S	■	E	■	N	■	A	■	A	■	O	■	N	■	L
9 O	K	R	A	S	■	10 S	T	R	I	C	T	U	R	E
P	■	S	■	U	■	E	■	E	■	■	■	S	■	M
11 H	12 O	T	■	13 R	E	S	14 T	R	I	15 C	T	■	16 H	E
17 A	T	E	■	E	■	■	E	■	■	L	■	18 A	■	N
G	■	19 D	Y	S	P	20 H	A	G	I	A	■	21 C	U	T
22 I	23 N	■	■	■	■	E	■	■	■	M	■	I	■	■
■	24 B	L	O	25 C	K	A	D	26 E	■	27 P	28 E	D	29 A	30 L
■	■	■	■	H	■	R	■	E	■	■	31 T	I	R	E
■	32 P	33 A	R	I	E	T	A	L	■	34 G	A	M	M	A
35 E	■	N	■	M	■	B	■	S	■	R	■	E	■	■
36 D	U	O	D	E	N	U	M	■	37 P	E	P	T	I	38 C
G	■	D	■	R	■	R	■	39 A	R	E	■	R	■	A
40 E	D	E	M	A	■	41 N	Y	L	O	N	■	42 Y	E	T